REMARKS/ARGUMENTS

Claims 1, 2, 8-12, 16-20, 26-30, 34-38, 44-47, and 49-52 remain in the application. Claims 1, 2, 11, 16, 17, 19, 20, 29, 34, 35, 37, 38, 44, 45, 46, 49, and 50 have been amended. Claims 15, 33, and 53 have been canceled. Reconsideration of this application, as amended, is respectfully requested.

Claims 1 and 19 have been amended to specify that the optical measurements in step (b) and step (e) are carried out by transmitting light into a region of the intact human tissue at a light introduction site and collecting light re-emitted from said region of intact human tissue at a light collection site, wherein the distance between a light introduction site and a light collection site is less than three millimeters. Claim 37 has been amended to specify that the apparatus comprises a source of light for irradiating a region of the intact human tissue with light at a light introduction site, a means for collecting light re-emitted from the region of the intact human tissue at a light collection site, wherein the distance between a light introduction site and a light collection site is less than three millimeters. Support for these amendments can be found at page 5, lines 24-26, at page 7, line 28 through page 8, line 5, and at page 22, lines 20-23 of the specification.

Claims 1, 2, 11, 16, 17, 19, 20, 29, 34, 35, 37, 38, 44, 45, 46, 49, and 50 have been amended to change "biological sample" or "sample" to "intact human tissue." Support for these amendments can be found in claims 1, 19, and 37.

Claims 1-2, 8-12, 15-20, 26-30, 33-38, 44-47, and 49-51 stand rejected under 35 U. S. C. §103 (a) as being unpatentable over U. S. Patent No. 5,978,691 to Mills in view of the journal publication "Effect of temperature on the optical properties of ex vivo human dermis and subdermis" by Laufer et al. in view of U. S. Patent No. 5,497,769 to Gratton et al. This rejection is respectfully traversed for the following reasons.

Mills, U. S. Patent No. 5,978,691 (hereinafter "Mills"), discloses a method for facilitating the noninvasive determination of characteristics of subject matter and the environment in which said subject matter exists, the method comprising the steps of:

Emitting at least one wavelength of electromagnetic radiation applied to said subject matter

Detecting said wavelength after contact with said subject matter

Inducing a temperature change in said subject matter while emitting and detecting said radiation applied to said subject matter

Computing parameters based on information processed from the contact of said radiation at various temperature levels on said subject matter.

Laufer et al., "Effect of temperature on the optical properties of ex vivo human dermis and subdermis" (hereinafter "Laufer et al."), discloses the effect of temperature on the optical properties of human dermis and subdermis as a function of near-infrared wavelength between 25 °C and 40 °C. Measurements were performed *ex vivo* on a total of nine skin samples taken from the abdomen of three individuals. Laufer et al. utilizes diffuse reflectance and transmission measurements carried out on thin dermis and subdermis samples at four different temperatures by means of an integrating sphere, which was placed in a temperature controlled environment. See page 2479 of Laufer et al.

Gratton et al., U. S. Patent No. 5,497,769 (hereinafter "Gratton et al. '769"), discloses the quantitative determination of various materials in highly scattering media such as living tissue in an external, photometric manner by the use of a plurality of light sources positioned at differing distances from a sensor. The light from the sources is amplitude modulated, and, in accordance with conventional frequency domain fluorometry or phosphorimetry techniques, the gain of the sensor is modulated at a frequency different from the frequency of the light modulation. Data may be acquired from each of the light sources at differing distances at a frequency which is the difference between the two frequencies described above. From these sets of data from each individual light source, curves may be constructed, and the slopes used to quantitatively determine the amount of certain materials present, for example oxyhemoglobin and deoxyhemoglobin in living tissue.

All of the claims of this application require spatially resolved diffuse reflectance measurements of intact human tissue. All of the claims of this application require that the biological sample be intact human tissue. All of the claims of this application require that the distance between (1) a light introduction site and (2) a light collection site be less than three (3) millimeters. See independent claims 1, 19, and 37, and the claims depending from independent claims 1, 19, and 37, especially part (b) of claim 1, part (b) of claim 19, and part (d) of claim 37 for spatially resolved diffuse reflectance measurements, and part (g) of claim 1, part (g) of claim 19, and part (b) of claim 37 for the requirement that the distance between (1) a light introduction site and (2) a light collection site be less than three (3) millimeters.

Spatially resolved diffuse reflectance measurements are described in detail at page 21, line 14 through page 22, line 3, and at page 31, line 9 through page 45, line 28 of the specification.

Mills fails to disclose spatially resolved diffuse reflectance measurements of any type of biological sample. Laufer et al., too, fails to disclose spatially resolved diffuse reflectance measurements of any type of biological sample. Furthermore, Laufer et al. fails to disclose measurements of reflectance of intact human tissue. In addition, Laufer et al. specifically teaches away from the measurement of optical properties in intact human tissue. While it is clear that both Mills et al. and Gratton et al. '769 disclose non-invasive processes that make use of intact human tissue, it is also clear that Laufer et al. does not and cannot make use of intact human tissue. According to Laufer et al., at page 2481, lines 8-9, of section *2.3. Measurement methods*:

> ".....Illumination of both sides of the sample was necessary as the samples of the dermis have different reflectivities from opposite sides....." (emphasis added)

According to Laufer et al. at page 2482, line 1 of section **3. Results**:

> "The optical coefficients were calculated for the front and back illumination of each sample....." (emphasis added)

According to these statements, there can be no doubt that the method of Laufer et al. is an invasive method that cannot be practiced on intact human tissue. According to Laufer et al., in order to measure the optical properties of the subdermis or deeper layers of the tissue, one must illuminate both sides of the sample, i.e., the front side and the backside. Such a manner of measurement would require that measurements be carried out on the exterior surface of human skin and underneath the layer of subcutaneous fat of human skin. In order to carry out the manner of introduction of light and collection of light from a region of human tissue as described in Laufer et al., the tissue must be excised from the human subject, and, consequently, the tissue **cannot** be intact human tissue. Breaching intact human tissue would completely defeat the purpose of the present invention, which is to measure optical parameters of intact human tissue non-invasively.

Gratton et al. '769 discloses an instrument having a sensor head 12 carrying eight light sources 22, 24 (individually labeled $D_1 - D_8$) with four each of the respective light sources 22 and 24 being positioned in separate rows so that the respective light sources 22 and the respective light sources 24 are each at different distances from a conventional light sensor 26. Light sources 22, 24 may be light emitting diodes, laser diodes, or any other light source system which is capable of being amplitude modulated at the desired frequency range. See column 5, lines 9- 17 of Gratton et al. '769. However, Gratton et al. '769 does not disclose the distances between the light sources and the light sensor. By closely reading Gratton et al. '769, it was learned that the distances typically used in the method described in Gratton et al. '769 could be found in Gratton et al, U. S. Patent No. 5,213,105. See column 7, lines 24-50, especially lines 39-50, of Gratton et al. '769 for reference to Gratton et al., U. S. Patent No. 5,213,105. According to Gratton et al., U. S. Patent No. 5,213,105, the distances between the light sources and the light sensor are in the range of at least two (2) centimeters, rather than in the range of less than three (3) millimeters. See FIG. 4A of Gratton, et al., U. S. Patent No. 5,213,105 and column 10, line 58 through column 11, line 28 of Gratton et al., U. S. Patent No. 5,213,105. The distances disclosed by Gratton et al., U. S. Patent No. 5,213,105, results in sampling the intact

human tissue at a depth ranging from two to five centimeters. Thus, the measurements performed by the method and apparatus described in Gratton et al. '769 are limited to measurements in deep layers in intact human tissue. At these depths, the temperature of the intact human tissue would be constant, and consequently, could not be modulated easily. If the temperature of the intact human tissue could not be readily modulated, the invention could not be carried out. In summary, (1) Gratton et al. '769 fails to disclose or suggest the use of localized reflectance geometry at small separations of light source and detector, in the absence of frequency modulation; (2) Gratton et al. '769 fails to disclose or suggest that temperature affects optical properties of intact human tissue; (3) Gratton et al. '769 teaches away from measurements at those depths of intact human tissue where modulation of temperature would be effective; (4) the method of Gratton et al. '769 cannot be used for measurements involving thin layers of skin tissue, esophageal tissue, or cervical tissue; (5) the method described in Gratton et al. '769 cannot be used with thin or superficial layers of tissue, where the thickness of the layers is on the order of less than three (3) millimeters, because the use of the apparatus required in Gratton et al. '769 would be likely to bring about complications in shielding the detectors and in processing of data.

Arakaki et al., U. S. Patent No. 5,931,779 (hereinafter "Arakaki et al."), was applied against claim 53 only. However, because the subject matter of claim 53 involved the distance between a source of light and a collector of light, the teachings of Arakaki et al. will be discussed in relation to the claims that recite a feature relating to separation of the source of light and the collector of light. Arakaki et al. discloses an optical spectrophotometer to acquire spectra between 515 and 660 nm. The light source was a 150-watt halogen bulb. A custom-made bifurcated fiber optic probe containing two fiber optic bundles was used to separately transmit light to and carry reflected light from the sample. The distal end of the probe is formed as illustrated in FIG. 2 by concentrically arranging separate fiber optic bundles; the central fiber optic bundle is 1.8 mm in diameter and carries light from the sample to the spectrograph and a 1.1 mm-diameter ring of fibers around the central bundle delivers light to the sample. The source and detection fiber bundles are thus

separated by a minimum distance of 1 mm. This separation results in a maximum sampling depth for visible light of about 1.8 mm. However, Arakaki fails to disclose the use of a plurality of distances between the fiber that transmits light to the sample and fiber that carries light from the sample to the spectrograph. Spatially resolved diffuse reflection measurements involve measurements of reflection at a plurality of sampling distances between light introduction sites and light collection sites for the determination of optical parameters, such as, for example, the absorption coefficient, the scattering coefficient, and light penetration depth in tissue. Thus, Arakaki does not contemplate spatially resolved diffuse reflectance measurements, and, consequently, would fail to remedy the deficiencies of Mills and Laufer et al. Furthermore, it would be impermissible to combine the teachings of Arakaki et al. with Gratton et al. '769, for the reason that it is impermissible within the framework of 35 U. S. C. §103 to pick and choose from any one reference only so much of it as will support a given position (i.e., a sampling distance of 1 mm), to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art (i.e., the use of only a single sampling distance, which would render the technique of spatially resolved diffuse reflectance impossible). The following table summarizes the results of the foregoing analysis and indicates how several of the references teach away from the claims of the present invention.

Reference	What reference fails to teach
Mills	Fails to disclose or suggest the technique of spatially resolved diffuse reflectance to determine optical parameters.
Laufer et al.	Fails to disclose or suggest measurements taken on intact human tissue.
Gratton et al. '769	Fails to require that distance between light source(s) and sensor(s) must be less than 3 millimeters. Teaches away from the use of temperature modulation to change optical properties of tissue.
Arakaki et al.	Fails to disclose or suggest the technique of spatially resolved diffuse reflectance to determine optical parameters.

Although each reference in the table discloses a particular feature of the claims of the present invention, it is impermissible within the framework of 35 U. S. C. §103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to

the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. For example, the type of measurements described in Mills and Arakaki et al. do not disclose and would not suggest to one of ordinary skill in the art the spatially resolved diffuse reflectance measurements used in the present invention. The biological samples disclosed by Laufer et al. are limited to those samples involving human tissue that is not intact; measurement of the non-intact human tissue samples described in Laufer et al. do not disclose and would not suggest to one of ordinary skill in the art the measurement of intact human tissue. Last, but not least, the distances between the light introduction sites and the light collection site described in Gratton et al. '769 do not disclose and would not suggest to one of ordinary skill in the art the distances between a light introduction site and a light collection site suitable for use in the present invention. The deficiency of Gratton et al. '769 is fatal to the ground of rejection because it teaches away from the use of temperature modulation of intact human tissue.

For the foregoing reasons, it is submitted that the combination of Mills et al., Laufer et al., and Gratton et al. '769 (along with Arakaki et al.) fails to render claims 1-2, 8-12, 16-20, 26-30, 34-38, 44-47, and 49-51, as amended, obvious to one of ordinary skill in the art.

Claim 52 stands rejected under 35 U. S. C. §103 (a) as being unpatentable over U. S. Patent No. 5,978,691 to Mills in view of the journal publication "Effect of temperature on the optical properties of ex vivo human dermis and subdermis" by Laufer et al. in view of U. S. Patent No. 5,497,769 to Gratton et al. '769, and further in view of U. S. Patent No. 5,873,821 to Chance et al. This rejection is respectfully traversed for the following reasons.

Chance et al., U. S. Patent No. 5,873,821 (hereinafter "Chance et al. '821"), discloses an oximeter disposed on an endoscope, catheter or guidewire or the like for insertion via a body passage to internal tissue, and including means such as an inflatable balloon to press the oximeter sensor against the localized tissue of interest.

Claim 37 requires that the biological sample be intact human tissue. Claim 52 depends from claim 37. Therefore, claim 52 requires all of the features of claim 37. Chance '821 fails to remedy the deficiencies of the combination of Mills, Laufer et al., and Gratton et al. '769, which were

described on pages 11-17 of this AMENDMENT AND RESPONSE. For the same reasons that claims 1-2, 8-12, 15-20, 26-30, 33-38, 44-47, and 49-51 are not obvious to one of ordinary skill in the art, claim 52 is not obvious to one of ordinary skill in the art.

Claim 53 stands rejected under 35 U. S. C. §103 (a) as being unpatentable over U. S. Patent No. 5,978,691 to Mills in view of the journal publication "Effect of temperature on the optical properties of ex vivo human dermis and subdermis" by Laufer et al. in view of U. S. Patent No. 5,497,769 to Gratton et al. '769, and further in view of U. S. Patent No. 5,873,821 to Chance et al. Claim 53 has been canceled. Accordingly, this rejection can be withdrawn.

In view of the foregoing, it is submitted that claims 1, 2, 8-12, 15-18, 19, 20, 26-30, 33-36, 37, 38, 44-47, and 49-52 are in condition for allowance, and official Notice of Allowance is respectfully requested.

Respectfully submitted,
O. S. Khalil, et al.

David L. Weinstein
Registration No. 28, 128
Attorney for Applicants

23492
Abbott Laboratories
D-377 AP6D-2
100 Abbott Park Road
Abbott Park, Illinois 60064-3500
Telephone: (847) 937-6182